Moving In Time: Neurons, Clocks, and Rhythmic Movements

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CHAPTER VIII

SUMMARY

Timing of movements is an integral aspect of human motor behavior. Rhythmic movements ranging from ordinary walking to playing a complicated piano piece rely heavily on correct timing. Even the simplest rhythmic movements are not without challenge; when the brain is affected by disease or injury, performing seemingly simple movements like walking can become quite a challenge. As all voluntary movements originate from neural signals produced by the brain, the investigation of timing naturally focuses on the brain. However, compared to the analysis of rhythmic movements, the analysis of brain signals associated with rhythmic movements is a rather difficult and hazardous affair. In moving only a single digit, many brain areas are involved in a complex interplay. In Chapter I, I discuss these issues in more detail and present a theoretical framework within which the techniques discussed in this thesis can be placed and interpreted in terms of the control and timing of movements.

As a starting point of this thesis, I decided to avoid the intricacies of the electrophysiology of the brain controlling timed movements, and depart from an abstract, mathematical model of the timing of movements based on theoretical concepts rather than highly detailed aspects of brain functioning. As humans are quite capable of producing rhythms at different tempos, many researchers have postulated that some kind of timer must reside somewhere in our brains. This timer is considered responsible for motor commands which eventually produce a response. Timer models have been employed to study the timing of movements that are synchronized to a metronome, that is, paced movements as well as self-paced movements. The simplest among those is the open-loop Wing-Kristofferson model, which consists of an internal timer or clock and motor delays that represent the time from the motor command to the time of the response. On the assumption that the timer intervals and the motor delays are independent, hierarchical processes that are similarly impacted by noise, the model predicts the temporal properties of rhythmic movements with remarkable accuracy.

The study reported in Chapter II discusses and extends the Wing-Kristofferson model. When tapping a desired frequency, subjects tend to drift away from this target frequency. This compromises the estimate of the correlation between inter-tap intervals (ITIs) as predicted by the Wing-Kristofferson model. Whereas previous studies on the timing of rhythmic tapping attempted to eliminate drift, the production of three constant frequencies (1.5, 2.0, and 2.5 Hz) was compared to the production of tapping sequences with linearly decreasing ITIs (corresponding to an increase in tapping frequency from 1.5 to 2.5 Hz). For all conditions, a synchronization-continuation paradigm was used. Tapping forces and electromyograms of the index-finger flexor and extensor were recorded and ITIs were derived yielding interval variability and model parameters, i.e. clock and motor variances. Electromyographic recordings served to study the influence of tapping frequency on the peripheral part of the tap event. The condition with an increasing frequency was more difficult to perform, as evidenced by an increase in deviation from the intended ITIs. In general, tapping frequency affected force level, inter-tap variability, model parameters, and muscle co-activation. Parameters for the condition with a decreasing ITI were comparable to those found in the constant frequency conditions. That is, although tapping with an intentional drift was different from constant tapping and more difficult to perform, the timing properties of both forms of tapping were strikingly similar and described quite well by the Wing-Kristofferson model.

Moving towards a more direct measurement of properties of the control of rhythmic movements, I investigated next the interaction between both hemispheres when unimanual movements are produced. It has been established that unimanual movements are not controlled solely by motor areas in the contralateral hemisphere, but rely on a bi-hemispheric interplay. When this interplay breaks down, mirror movements may be observed. Mirror movements are traditionally described as unintentional activity of the muscles homologous to those involved in a unimanual movement. By studying the dynamics of mirror movements, the timing of unimanual movements and the interplay between both hemispheres can be investigated.

The experiment presented in Chapter III focusses dynamical properties of mirror movements. Using a rhythmic isometric force production paradigm, after-effects of in-phase and anti-phase bimanual performance on the unintended recruitment of the homologous muscles of the opposite limb during subsequent performance of unimanual tasks were

investigated. Electromyograms obtained from the muscles of the opposite limb were analyzed in terms of their amplitude and the distribution of their phase relative to that of the intended movements. Preceding bimanual activity had distinct effects on the relative phase (mean and uniformity) of the structured electromyograms. These were particularly pronounced following performance of the in-phase pattern. These findings were discussed in terms of possible mechanisms of interhemispheric excitation and inhibition.

In many systems, great insight is gained by analyzing the system's behavior during perturbations. Obviously, perturbing the brain poses ethical problems. However, as the timing of movements is affected by diseases such as Parkinson's disease (PD), one may consider the Parkinsonian brain as a perturbed healthy brain. In PD patients, a major component in the generation of rhythmic movements, the basal ganglia, is disrupted. Besides the familiar tremor, motor problems such as shuffled or unstable gait and initiating movements increase progressively. As the basal ganglia and the motor areas are directly and indirectly coupled, the changes in the basal ganglia extend to the motor areas that can be investigated using MEG. Unfortunately, PD is not a curable disease. Thus much effort has been put into developing methods to reduce the symptoms of PD. Great advances have been made in reducing some of the characteristic motor problems associated with PD. Recently, for instance, a therapy has been successfully implemented that uses external rhythmic cues to help improve the motor performance and timing of PD patients. As part of a large study investigating the effects of cueing therapy, a paradigm involving cued and self-paced movement was performed at the MEG facility of VU Medical Center. These data were analyzed in Chapters IV and V.

Parkinson's disease is characterized by motor and cognitive problems that are accompanied by slowing of neural activity, even in early stage PD. Slowing is typically studied during resting state. Chapter V extends the study of this phenomenon from resting state to movement by comparing the relationship between neural slowing and disease severity during rest and motor performance. Primary motor activity was assessed by means of magnetoencephalography (MEG) during rest and rhythmic movements. Motor output and event-related cortical power in the alpha and beta frequency bands were determined. UPDRS total and subscores were used to pinpoint the predictors of neural slowing (change of power toward slower frequencies) during both resting state and the production of rhythmic movements. By design, motor performance was similar for patients and controls. PD

patients showed slowing of neural activity which increased with disease severity. Slowing during rest was best predicted by the cognitive subscore, whereas slowing during movement was best predicted by the motor subscore. These results suggest that slowing is functionally modulated and that different mechanisms are responsible for neural slowing during rest versus movement. Neural slowing must be viewed in a broader context than previously thought because it is not solely related to impaired motor performance but also impaired cognition.

PD not only affects the ability to move in a controlled manner, but also the ability to change behavior. A striking example is 'freezing' where a patient wants to start walking only to find him- or herself unable to move. Once a patient begins to walk, termination of this movement can also be affected. In light of the problems of switching from one type of behavior to another, after-effects of rhythmic activity can give insight into the way rhythmic movements are processed in the Parkinsonian brain and how the beneficial effects brought about by cueing therapy facilitate switches.

Chapter IV reports a study of the effects of Parkinson's disease on the production of rhythmic movements. External rhythmic cueing is known for its capacity to improve motor performance in PD patients. The neural correlates of these beneficial effects, however, are largely unknown. We examined the cortical activity accompanying rhythmic force production under two types of tactile cueing, regular and irregular, using MEG, and expected the cortical activity in the alpha and/or beta frequency range to respond differently to the different types of cueing, in the absence of differences in motor performance. Twenty early-stage Parkinson patients and fifteen age-matched healthy controls performed series of cued and self-paced rhythmic movements separated by rest. Each series was performed in the presence of regular or irregular cues. Using linear beamformers, MEG recordings revealed dominant motor-related activity in bilateral M1s. We found increased beta activity during the post-performance resting state compared to the pre-performance resting state. This beta rebound lasted 5 to 10 s in PD patients and controls alike and its strength depended on the presence of cueing and its type. In addition, we found a late and more sustained effect in the alpha band where the amplitude increased 40 s after movement termination. Although the quality of motor performance was similar for patients and controls, the after-effect in the alpha band was absent in the PD patients. It was thus concluded that motor perseverance is responsible for the absence of the increase in alpha power in PD patients.

Chapter VI summarizes the findings of the thesis and discusses them in light of current theories on the timing of movements. The validity and falsification of timer models is discussed in terms of experimental designs involving transcranial magnetic stimulation and the use of subdural electrodes in the brain. In addition, the results of the MEG studies reported in this thesis are compared to results using more invasive techniques and possibilities for future research are discussed.

Coda: this thesis first discussed the Wing-Kristofferson model for the timing of repetitive movements. The behavioral and encephalographic results discussed in Chapters II through V suggested that the timer in this model is rather oversimplified. Motor timing emerges from the interplay between different brain areas and capitalizes on the bilateral organization and interconnectivity of both hemispheres. The timer is thus not a fixed entity located somewhere in the brain, but exists by grace of a large dynamic network involving a large part of the brain. Therefore, gaining access to the timer and its properties is limited, constraining us to view this multifaceted object only one side at a time. Aggregation of the findings of this thesis and the aforementioned discussion will set the stage for future directions of research.